SYNOPSIS

TITLE OF TRIAL

A randomized, double-blind, placebo-controlled, infusion proof-of-concept trial investigating the safety, tolerability, pharmacokinetics, and pharmacodynamics of ascending doses of FE 202158 in patients with vasodilatory hypotension in early septic shock

SIGNATORY INVESTIGATOR

[redacted]

TRIAL SITE(S)

Denmark: Rigshopitalet, Hvidovre Hospital, Hillerød Hospital, Bispebjerg Hospital
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PUBLICATION (REFERENCE)

N/A

TRIAL PERIOD	**CLINICAL PHASE**
First patient first visit: 25 November 2009 Last patient last visit: 14 September 2011	II

OBJECTIVES

Primary objective

- Establish proof-of-concept for specific V1a agonism in patients with vasodilatory hypotension in early septic shock (stabilisation of adequate blood pressure)

Secondary objectives

- Assess the pharmacokinetics of FE 202158 in patients with vasodilatory hypotension in early septic shock
- Assess the pharmacodynamic effects of FE 202158 with special focus on blood pressure, vascular leakage and inflammatory response.
- Detect early signals suggestive of clinical efficacy of FE 202158 (morbidity and mortality)
- Assess the safety and tolerability of FE 202158 in patients with vasodilatory hypotension in early septic shock

ENDPOINTS

Primary endpoints

Stabilisation of blood pressure

- Proportion of patients maintaining target MAP with no open label NE at 12 hours, 24 hours, 48 hours, 96 hours and Day 7

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- Cumulative dose and infusion rates of open label NE (every 12 hours for 3 days, then daily)

Secondary endpoints

Pharmacokinetics:

- Pharmacokinetic parameters of FE 202158: CL, Vss, t½

Pharmacodynamics:

- Blood pressure: Changes in SBP, DBP and MAP
- Heart rate
- Inflammatory response:
- Change in C-reactive protein (CRP) at 24 hr, 48 hr, 96 hr and 7 days
- Change in TNFα, IL-6, IL-10, IL-1ra

Effect on vascular leakage

- Change in albumin at 6, 12, 18, 24, 48, 96 hr and 7 days
- Change in hematocrit at 6, 12, 18, 24, 48, 96 hr and 7 days
- Change in fluid balance every 6 hours for the first 3 days and then twice daily for (up to) 7 days

Safety and tolerability

Changes in:

- Vital signs (blood pressure, heart rate, and body temperature)
- Mean arterial pressure, central venous pressure
- ECG (intervals, rhythm, and morphology)
- Pulmonary function (tidal volume, PaO2/FiO2)
- Arterial blood gases and lactate, oxygen saturation in vena cava superior: Scvo2
- Clinical chemistry, haematology, haemostasis, urinalysis
- Adverse events (type, frequency, and intensity).

Morbidity:

- Time course of SOFA scores
- Days alive and free (DAF) of organ dysfunction using the SOFA score at day 7, 14 and 28
- Proportion of patients who were alive and off all vasopressors at day 7, 14 and 28
- Days alive and out of ICU at day 7, 14 and 28
- Days alive and free of vasopressors, corticosteroids for sepsis treatment, dialysis, or assisted ventilation at day 7, 14 and 28
- Length of stay and alive in ICU up to Day 28
- Length of stay and alive in hospital up to Day 28

Mortality:

- Mortality rate at 24 hr, Days 7, 14, and 28

METHODOLOGY

This was a double-blind, randomised, placebo-controlled continuous infusion trial investigating three ascending infusion rates of FE 202158 in patients with vasodilatory hypotension in early septic shock. A new cohort of subjects was used for each dose panel. An independent unblinded Data Monitoring Committee evaluated the safety and tolerability of each dose to determine whether the dose should be increased according to the dose-escalating schedule, repeated, decreased to the previous dose, or whether dosing should be stopped.

FE 202158 or placebo was administered to patients for up to 7 days at rates that kept the mean arterial pressure within 65-75 mmHg. Concomitant open-label norepinephrine was administered and adjusted to maintain the mean arterial pressure within the target limits if administration of IMP was not sufficient, but was decreased and stopped during the course of the trial, if possible. Assessments were scheduled during the 7-days treatment period, and after the treatment period on Days 15 and 28.

NUMBER OF SUBJECTS

55 subjects were screened of whom 53 were randomised and 52 dosed. Subjects not assessed on Day 28, for whatever reason, are regarded as 'not completed'.

	1.25 ng/kg/min	2.5 ng/kg/min	3.75 ng/kg/min	Placebo	Total
Planned	10	20	10	20	60
Randomised	10	19	2	22	53
Dosed	10	19	2	21	52
Completed	5	16	0	15	36

MAIN CRITERIA FOR INCLUSION / EXCLUSION

Patients of both sexes, at least 18 years of age with vasodilatory hypotension in early septic shock, i.e. proven or suspected infection, hypotension, signs of tissue hypoperfusion, not responding to fluid, and requiring vasoconstrictor treatment, could be included in this trial. Specific requirements defining early septic shock were systolic blood pressure less than 90 mmHg or decrease in systolic blood pressure by at least 40 mmHg for more than one hour, not respondeding to 20 ml/kg of crystalloid or 10 ml/kg of colloid, requiring norepinephrine at a dose of at least 0.1 μg/kg/min for at least 2 hours. Initiation of infusion had to commence within 24 hours of fulfilling inclusion criteria. Patients with underlying chronic heart disease, vascular disease, traumatic brain injury, hyponatremia, or anticipated near death, were not eligible.

MEDICINAL PRODUCTS

IMP
FE 202158 (0.1 mg/ml, 10 mM acetate buffer, pH 4) or placebo. FE 202158 was provided as a stock solution which was diluted with saline prior to infusion according to specific dilution protocols. Saline was used as placebo. FE 202158 was infused intranvenously at initial rates of 1.25, 2.5, and 3.75 ng/kg/min.

Non-IMP
Levophed (noradrenaline tartrate) 40 μg/ml, infused at a rate necessary to keep the mean arterial pressure within target of 65-75 mmHg

DURATION OF TREATMENT

Each subject could receive up to 7 days of intravenous infusion of FE 202158 or placebo.

TRIAL PROCEDURES / ASSESMENTS

Patients with vasodilatory hypotension in early septic shock were randomised to a constant intravenous infusion of placebo or FE 202158. Three initial infusion rates of FE 202158 were investigated in a dose escalation scheme. The initial infusion rates of the three FE 202158 cohorts were 1.25 ng/kg/min, 2.5 ng/kg/min, and 3.75 ng/kg/min, respectively. A fourth cohort was a repetition of the 2.5 ng/kg/min group.

Open label NE was adjusted as necessary to maintain the target MAP. When patients were hemodynamically stable, open label NE was tapered off first and if MAP remained stable for 4 hr in the absence of open label NE, stepwise weaning of the study drug, as tolerated by MAP, commenced.

If weaning resulted in hemodynamic instability, i.e. MAP falling below target limits, the study drug was re-instituted first. If patients remained hemodynamically unstable, open label NE was reinstituted. Study drug infusion was continued as long as blood pressure support was deemed necessary but no longer than 7 days. Patients who still needed vasopressor support after 7 days were switched over to open label NE or other vasopressor to maintain target MAP.

Assessments reflecting the endpoints were performed throughout the treatment with IMP and subsequently at specified time points.

STATISTICAL METHODS

Sample size:

The trial size provides a basis for a first safety and tolerability assessment in the target patient population. Proof of concept will be based on the overall interpretation of statistical analyses of endpoints.

Pharmacokinetics analysis:

PK parameters were estimated using nonlinear mixed effects compartmental PK modelling.

Pharmacodynamics and efficacy analysis:

Confidence intervals were calculated reflecting the proportion of patients alive and stabilised without open label NE, supplemented by Bayesian methods (beta-binomial posterior distribution, using non-informative prior distributions).

Confidence intervals were calculated reflecting the proportion of patients alive and stabilised, supplemented by Bayesian methods (beta-binomial posterior distribution, using non-informative prior distributions). Data were analysed using a logistic regression model, presenting odds ratio comparisons of the FE 202158 groups to placebo. There were two analyses, one adjusting for the rate of open label NE administered, and one with no adjustment reflecting the effect of FE 202158 as an add-on drug.

The mean amount of open label NE administered, both in terms of rates and total amount administered, was calculated as well as the proportion of patients actually receiving open label NE (categorised by amount), thereby also reflecting the number of patients lost between the time intervals. The FE 202158 groups were compared individually to the placebo group in an ANOVA model.

Changes in serum albumin, hematocrit, cytokine levels, CRP and fluid balance were analysed by ANCOVA, adjusting for the respective baseline value.

Frequency tables of all morbidity endpoints were constructed per treatment group. Confidence interval of location parameter differences were based on the non-parametric Hodges-Lehmann method.

Confidence intervals (Clopper-Pearson) for mortality rates were calculated.

EFFICACY RESULTS

The evaluation of the efficacy showed that FE 202158 could substitute for norepinephrine in the treatment of septic shock. At 12 and 24 hours after start of treatment the proportion of subjects needing NE was statistically significantly lower with 2.5 ng/kg/min FE 202158 compared to placebo, as was the difference in infusion rate of NE during the first 36 hours. The cumulative dose of NE decreased in an FE 202158-dose dependent manner, the difference between 2.5 ng/kg/min and placebo being statistically significant from 36 hours and on. The Kaplan-Meyer graph of time to shock resolution indicated a higher probability of shock resolution with the 2.5 ng/kg/min treatment compared to 1.25 ng/kg/min and placebo during the first 2-3 days.

2.5 ng/kg/min FE 202158 showed a positive effect on the net cumulative fluid balance compared to placebo, which was statistically significant from Day 5 on. Data indicated this difference may be due to decreased need for fluid administration rather than increased fluid output.

The mean time of 'alive and free of assisted ventilation' was statistically significantly longer for the 2.5 ng/kg/min group compared to the placebo group.

The pharmacokinetic evaluation showed that the steady state concentration was dose proportional to the infusion rate and reached after approx. 7 hours of infusion. The terminal half-life was approx. 2.5 hours, while the initial half-life was much shorter, approx. 10 min.

There were no other significant differences between active treatment and placebo in any other pharmacodynamic or morbidity parameter, or mortality.

SAFETY RESULTS

There were no apparent differences between treatment with FE 202158 and placebo with respect to adverse events, serious adverse events, or intensity of adverse events. The ADRs occurring in the active treatment groups, e.g. peripheral ischaemia, could generally be attributed to exaggerated pharmacological vasoconstrictor effects. Evaluation of the vital signs, ECG, clinical chemistry, haematology, haemostasis, and urinalysis parameters did not indicate any differences between active treatment and placebo. Neither were there any indications of differences in pulmonary function, blood gases, lactate, or oxygen saturation. Thus, administration of FE 202158 to patients in septic shock appeared to be safe and well tolerated.

CONCLUSIONS

- FE 202158 was able to substitute for norepinephrine in a dose dependent manner in maintaining an adequate blood pressure, thus establishing proof of concept for specific V1a agonism
- 2.5 ng/kg/min FE 202158 significantly increased the time alive and free of ventilation compared to placebo
- 2.5 ng/kg/min FE 202158 decreased the cumulative fluid balance compared to placebo
- 2.5 ng/kg/min FE 202158 tended to increase the probability of early shock resolution compared to placebo
- No effects were observed by FE 202158 with regards to inflammatory biomarkers, SOFA score, or organ dysfunction (except for assisted ventilation)
- No effects were observed by FE 202158 on length of stay in ICU or hospital
- No effects were observed on mortality
- The steady state plasma concentration of FE 202158 was proportional to the infusion rate
- The clearance, initial elimination half-life and terminal half-life of FE 202158 in septic shock patients were approx. 10-13 L/h, 10 min, and 2.5 hours, respectively
- No drug-specific trends in occurrence of AEs or negative effects related to vital signs, ECG, liver or kidney function, or other organs were observed.